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| 09/741,272 | 12/19/2000 | Charles Raymond Degenhardt | 8371 | 6508 |

27752 7590 10/29/2002

THE PROCTER & GAMBLE COMPANY
INTELLECTUAL PROPERTY DIVISION
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CINCINNATI, OH 45224

EXAMINER

MCKENZIE, THOMAS C

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1624

1)

DATE MAILED: 10/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/741,272

Applicant(s)

DEGENHARDT ET AL.

Examiner

Thomas McKenzie Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 August 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,4,5,9,11 and 18-31 is/are pending in the application.
- 4a) Of the above claim(s) 5 and 9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,4,11,18-23,25-27 and 29-31 is/are rejected.
- 7) ☒ Claim(s) 24 and 28 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 8/29/02. Applicants have amended claims 18 and 29-31. There are nineteen claims pending and under consideration. Claims 2, 4, 5, 9, 11, and 18-24 are compound claims. Claims 25-28 are composition claims. Claims 29-31 are use claims. This is the third action on the merits. The application concerns some 2-piperidinylcarbonyl-piperidines.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/29/02 has been entered.

Election/Restrictions

3. Claims 2, 4, 5, 9, 11, 18-23, and 25-31 are generic to a plurality of disclosed patentably distinct species comprising different heterocyclic rings A, distinct linking groups R⁴ and distinct terminating groups R⁵. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the

record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

4. During a telephone conversation with Kelly McDow-Dunham on 10/25/02 a provisional election was made with traverse to prosecute the invention of species number 7, on page 34, with is also the first pictured compound in claim 24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5 and 9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species. The elected species has $R^4 = CH(R^1)$ and claims 5 and 9 are drawn to different R^4 group.

According to the MPEP 803.02, "On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered

obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.”

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Response to Amendments

6. Applicants’ amendment of claims 29-31, listing more than two conditions to be treated, and two transport proteins to be inhibited overcomes the indefiniteness rejection made in #5 of the previous office action. To expedite prosecution, the enablement rejection made in point #7 of the previous office action is withdrawn. Applicants’ amendment to claims 29-31, limiting the transport proteins to MRP1 and p-glycoprotein in mammals requiring such treatment overcomes the

enablement rejection made in point #9, but please see the indefiniteness rejection made below.

Claim Objections

7. Claim 26 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim or amend the claim to place the claim in proper dependent form. Claim 25 is drawn to the compounds of claim 18. Claim 26 is drawn only to the active compounds of claim 18. Since protein transport inhibition is the only activity ascribed to the compounds, which compounds of claim 18 lack this property? Line 16, page 7 says only that “active compounds can have the structure [of claim 18]”. If there are compounds of the formula given in claim 18 lacking any such activity, the Examiner requests that they be identified so that the proper utility rejection may be made.

Claim Rejections - 35 USC § 112

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 2, 4, 11, 18-23, 25-27, 29, and 30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases “about 10”, “about 4”, and “about 9” in claim 18 are indefinite. The ring A must contain a positive whole number of

members. Does “about 10” mean ten atoms or could it mean eleven? How about fifteen?

Applicants argue that there is no case law prohibiting “about” in claims. They argue that the term has been used before in other patents. Finally, Applicants argue that the specific technical facts govern the use of “about” in claims. The first two issues have been discussed previously. Concerning the final point, the Examiner hardly agrees. Applicants are confusing discrete with continuous variables. Atoms only occur in discrete units, unlike process variables like temperature, pressure or spatial variables like a diameter. There is no such thing as 10.1 or 9.9 atoms. Since 9.9 atoms would violate the laws of chemistry, Applicants insistence on “about” indicates that ten atoms are not being claimed but Applicants do not place any upper bound on their intention. The specific technical fact that atoms occur in whole units requires that Applicants meaning be considered unclear.

9. Claims 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims provide for the use of the compounds of claim 18 and the compositions of claim 11 and 24, but the claims do not set forth any steps involved in determining how to identify “a mammal in need

of” “inhibiting p-glycoprotein, inhibiting MRP1”. It is unclear what diseases and treatments applicant is intending to encompass.

Lines 21-26, page 1, lines 11-14, page 2, and lines 9-26 page 14 discuss why one would inhibit MRP1 and Pgp but only in the context of treating multi-drug resistance. Are the only mammals requiring this inhibition suffering from multi-drug resistance? If so, why list the diseases separately? Alternatively, if there are additional diseases Applicants wish to treat, what are they?

The Examiner suggests claiming treatment of multi-drug resistance.

10. Claims 2, 4, 11, 18-23, 25-27, 29, and 30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrases “amide”, “ester”, and “imide” “susceptible to being cleaved in vivo by a mammalian subject” are unduly functional. What are the structures of these claimed compounds and how does one determine if they are so cleavable? It is not proper to describe compounds by their principal biological property, when more precise ways, i.e. names and structures are available.

Applicants have replaced the word “biohydrolyzable” by the phrase “susceptible to being cleaved in vivo ... “. Search using the search engine at <http://www.scirus.com/> for “amide and the phrase “cleaved in vivo” gave fourteen hits, only four of which were relevant. Two involved compounds that were prodrugs of amides, not Applicants’ intention. The other two “Enzyme-catalyzed prodrug approaches for the histamine H3-receptor agonist”, Stark, H. et al, Bioorganic and Medicinal Chemistry, Jan 2001 and “A Novel Series of Orally Active Antiplatelet Agents”, Zablocki, J.A. et al, Bioorganic & Medicinal Chemistry, May 1995 disclosed two structurally unrelated amides that were cleaved *in vivo*. Thus, the skilled medicinal and chemist would not understand what amides were being claimed and it is strictly phenomenological whether any specific amide is so cleaved. That is, it depends strictly on the structure of the rest of the molecule and no generally recognized list of such amides exists.

Functional language is proper where there is an art-recognized correlation between the chemical structure being claimed and the biological function being asserted. In the present case, Applicants have not made that assertion nor is such a correlation between structure and function art-recognized as well understood. According to the MPEP §2162 “The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of

species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.”

11. Claims 2, 4, 11, 18-23, 25-27, 29, and 30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The proviso in the last line of section (f) of claim 18, concerning the relationship between R^4 and R^5 lacks description. Nowhere in the specification is such a relationship linking the description between the two radicals described. The concept of linking the value of r to the specific divalent radical present as R^4 is not present. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: “we agree with the examiner's position of record that the negative limitations

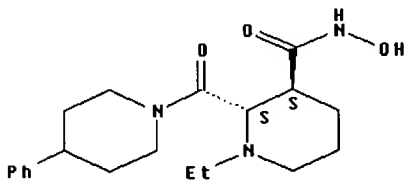
recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.” “It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts.” Please also see the anticipation rejection over Xue (WO 99/65867) made below.

Applicants argue that they have possession of the remaining embodiments of their invention remaining after the proviso is considered. They also point to some specific working examples to illustrate their point. This is true but not germane to the rejection. The issue is making a connection between allowed values of variables, when that connection was not present verbatim as filed. Until the Examiner made the anticipation rejection, the Applicant had no reason to single out the species embraced by the provisos. When filed, the application did not recognize that species as special, nor is the Applicant now claiming that he recognized it as so. The U.S. Court of Appeals affirmed the Grasselli decision for the Federal Circuit in an unpublished memorandum opinion, 738 F.2d (1984). A proviso, excluding one species from a Markush group of 56, was held to lack description since it was not in the specification as filed.

The fact situation in Grasselli is the same, as the present application, namely that a specific Markush species was not excluded until the Examiner drew attention to it. Nowhere in the present specification or original claims is the species embraced by the provisos mentioned either positively or negatively. It is not mentioned as a preferred embodiment. The proviso provided by the Applicant is by definition a negative limitation. The species defined by the proviso is treated differently than similar species. The special nature of that species was not apparent to the Applicant at the time of filing and if it were now introduced, would constitute new matter. Thus, the proviso introduces a new concept.

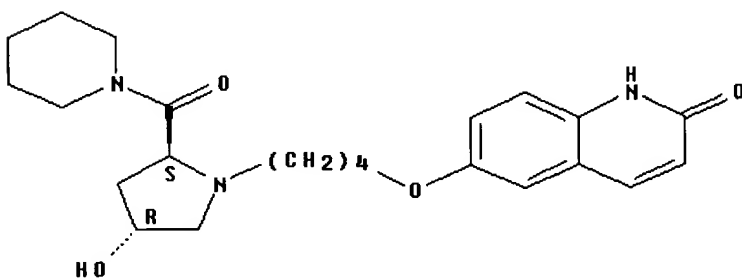
Claim Rejections - 35 USC § 102

12. Claims 2, 4, 11 18, and 25-27 remain rejected under 35 U.S.C. 102(b) as being anticipated by Xue (WO 99/65867). There are six compounds in this reference that anticipate Applicants compound claims, one of which is shown below. It has $R^5 = O_rR^6$, $r = 0$, $R^6 =$ the hydrocarbon group methyl, $t = 0$, $R^4 = CH(R^1)$, $R^1 =$ hydrogen, $A =$ piperidine, $w = 1$, $R^8 =$ N-hydroxy-3-carboxamide, $x = 0$, and $NR^2R^3 = 4\text{-phenyl-1-piperidinyl}$. The compound is described in the table on page 108 and is compound 75. Please also see claims 5 and 7 of this reference.



Applicants' proviso in the last line of section (f) of claim 18, concerning the relationship between R^4 and R^5 and discussed above excludes the art disclosed by Xue (WO 99/65867). However, this proviso constitutes new matter and the rejection is maintained.

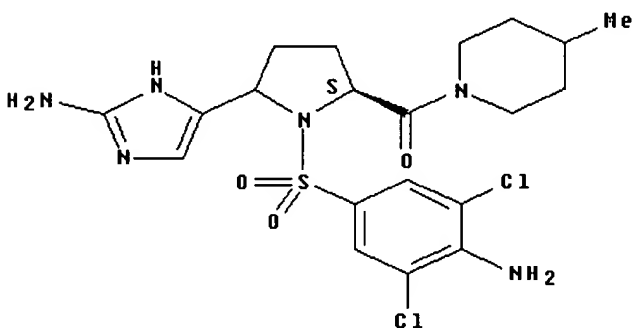
13. Claims 2, 18, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato ('239). There is one compound in this reference that anticipates Applicants compound claims, which is shown below. It has $R^5 = 4-[(1,2\text{-dihydro-2-oxo-6-quinolinyl})\text{oxy}]\text{butyl}$, $R^6 = (1,2\text{-dihydro-2-oxo-6-quinolinyl})\text{oxy}$, $r = 1$, $t = 3$, $R^4 = \text{CH}(R^1)$, $R^1 = \text{hydrogen}$, $A = 4\text{-hydroxy-2-pyrrolidinyl}$, $w = 1$, $R^8 = 4\text{-hydroxy}$, $x = 0$, and $\text{NR}^2\text{R}^3 = 1\text{-piperidinyl}$. The compound is described in Example 74, lines 31-45, column 70.



The Examiner indicated in the previous office action that Applicants requirement that the piperidine ring formed by R^2 and R^3 be substituted overcame the rejection

over Sato ('239). That substitution requirement is in claim 4. Thus, the parent claims are still anticipated.

14. Claims 2, 4, 18, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Grell (DE 195 48 797 A1). There are three compounds in this reference that fit the formula of claim 18. One compound, which is shown below, has registry number 193018-74-5. It has $R^5 = R^6 = 4\text{-amino-3,5-dichlorophenyl}$, $r = 0$, $t = 0$, $R^4 = \text{SO}_2$, $A = 2\text{-amino-1H-imidazol-4-yl-2-pyrrolidinyl}$, $w = 1$, $R^8 =$ the substituted heteroaromatic group $2\text{-amino-1H-imidazol-4-yl}$, $x = 0$, and $\text{NR}^2\text{R}^3 = 4\text{-methyl-1-piperidinyl}$. The compound is described in Example 23, lines 24-43, page 34. Claim 10 of the reference teaches compositions ("Arzneimittel").



Allowable Subject Matter

15. Claims 24 and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 31 would be allowable if rewritten to overcome the rejection under 35 U.S.C. 112, second

paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

16. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

 **Mukund Shah**
Supervisory Patent Examiner
Art Unit 1624

TCMcK
October 28, 2002




BRUCK KIFLE, PH.D.
PRIMARY EXAMINER